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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,442	10/04/2004	Klaus Braun	4121-171	3755

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EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
07/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,442	BRAUN ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8,10-15,19,20 and 22-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,10-15,19,20 and 22-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Applicants' amendment filed on 04-03-2008 has been entered.
3. Status of claims. Claims 1-3, 8, 10-15, 19, 20 and 22-35 are currently pending. Claims 1, 8 and 20 have been amended; claims 4, 7, 18 and 21 have been canceled and claims 30-35 have been added by applicants amendment filed on 04-03-2008.
4. Applicants elected to prosecute with traverse in the response filed on 01-16-2007 the following species c-myc as the specifically named mRNA, Gadolinium (Gd) as the specifically named diagnostic conjugate and Polylysine as the specifically named spacer. The restriction requirement among the following species c-myc, c-ras, hern, sst1, sst2 was previously withdrawn. Accordingly, the instant claims are examined to the extent that they read on the elected species of Gd and Polylysine as the generic claim is not allowable.
5. Therefore, claims 1-3, 8, 10-15, 19, 20 and 22-35 are currently being examined to which the following grounds of rejection are applicable.

Withdrawn rejections in response to Applicant arguments or amendments.

Claim Rejections - 35 USC § 112- Second Paragraph

In view of Applicants' cancellation of claim 21, rejection of claim 21 under 35 U.S.C. 112, second paragraph, is rendered moot.

35 USC § 112- First paragraph- Written description

In view of applicants amendment of claim 1 and 20 to identify a grop of "cell-penetrating transport peptides" as the transmembrane module, a group of peptide nuclei acid (PNA) antisense to and hybridizing with a mRNA selected from a group of c-myc-mRNA, c-ras-, hern-, sst1 or sst2-mRNA as the address module , and a genus of compounds trapping Gadolinium as the signaling module, rejection of claim Claims 1-3, 8, 10-15, 19, 20 and 22-29 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, has been withdrawn.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Claim Rejections - 35 USC § 102(e)

In view of the earliest effective filing date of the claimed subject matter of the present application to the foreign priority date of January 22, 2002, and further in view of Collin's (US Patent Application Publication No. 2006/0074034) claimed priority to provisional applications 60/322,861, filed on Sep. 17, 2001 and 60/410,627, filed on Sep. 13, 2002, wherein the disclosure of the provisional application 60/322,861, filed on Sep. 17, 2001 does not correspond to the claimed subject matter of US Patent Application Publication No. 2006/0074034, rejection of claim 1-3, 15 and 19 under 35 U.S.C. 103(a) as being 35 U.S.C. 102(e) as being anticipated by Collins et al, US Patent Application Publication 2006/0074034, Date of Publication April 6, 2007) is withdrawn.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Rejections maintained in response to Applicant arguments or amendments.

Claim Rejections - 35 USC § 112- First paragraph- Scope of Enablement

Claims 1-3, 8, 10-15, 19, 20 and 22-29 remain rejected and new claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A diagnostic conjugate for the molecular imaging of a human tumor expressing a c-myc, c-ras, hern, sst1 or sst2 gene comprising in sequential order:

> a transmembrane transport peptide of SEQ ID Nos. 2, 3 or 4, conjugated via a cleavable linker to the a peptide nucleic acid which hybridizes with a c-myc, c-ras, hern, sst1 or sst2 mRNA, conjugated via a linker to a $Gd3^{+}$ complex, wherein said target specific antisense conjugated $Gd3^{+}$ transporter complex is transported across the cell membrane, wherein a hybrid is formed of said an antisense peptide nucleic acid and the RNA target sequence, wherein said hybrid begins to be slowly enzymatically cleaved, thereby releasing the target specific antisense conjugated $Gd3^{+}$ transporter,
>
> does not reasonably provide enablement for a diagnostic conjugate as broadly claimed.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

The Examiner refers Applicants to the reasons of record, as disclosed in the previous office action filed on 10-09-2007. In addition new claims 32-35 raise enabling issues in relation to a cell penetrating peptide of human origin which can penetrate the plasma membrane. Thereby, specific issues in relation to the functional domains in any cell- penetrating peptide of human origin critical for cell penetration have to be examined and considered for patentability regarding the broadly claimed methods. In relation to a "transmembrane module" (TPU), Applicants disclose in the specification that preferred TPUs are derived from the penetratin family or transportan, and discloses three peptides of SEQ ID Nos. 2, 3 and 4 as TPU that are coupled to the address module (AS) via a covalently cleave spacer I (p. 6, last paragraph) resulting in the products Nos. 3723, 3724 and 3725 (Table 1, column of product No.). The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry John Wiley and Sons, 1990, p. 126-129). Since, the relationship between a sequence of a peptide and its tertiary structure is not well understood and is not predictable, it would required undue experimentation for one skilled in the art to arrive at other cell-penetrating peptides of human origin that can function as a transmembrane transport unit to target specific antisense conjugated $Gd3^{+}$ transporter complex across the cell membrane.

Response to Applicants' arguments as they relate to rejection of 1-3, 8, 10-15, 19, 20 and 22-35 are rejected under 35 U.S.C. 112, first paragraph-scope of enablement.

At page 14 of remarks, in relation to a genus of cell-penetrating transport peptides capable of penetrating the plasma membrane, Applicants cite that "At the filing date of the application, those of skill in the art were aware of the transport peptides that are embraced by the expression "cell penetrating transport peptides which penetrate the plasma membrane," as including a group of peptides that translocate across the plasma membrane by an energy-independent and receptor-independent mechanism. Penetratin and transportan are illustrative of such known and well-established peptides. Numerous transport peptides of this group, as well as their capability to internalize various cargo-molecules into a cell, were reported in the various publications identified above. (See Exhibits A, B, D-H) ". Moreover Applicants allege that "With respect to the "penetratin" and "transportan" variants, analogs and structure-activity relationships were reported that included the sequences responsible for the translocating capability. (See Exhibit A, E, the Lindgren et al. articles; Exhibit B, Soomets et al.; and Exhibit D, by Fischer et al.)" As such, Applicants argue that a person of skill in the art is enable to make conjugates according to the invention with a cell-penetrating transport peptide other than SEQ ID NOs: 2, 3 or 4, without any undue burden". Such is not persuasive.

The instant diagnostic conjugates are generated for tumor imaging requiring the linkage of the Antennapedia third helix thought disulfide bonds to an antisense peptide nucleic acid which specifically hybridizes to the corresponding RNA target. The linkage of the PNA to a transmembrane transport peptide of SEQ ID Nos. 2, 3 or 4 is critical in order to release the PNA in the cytoplasm, as the disulfide bond breaks, thereby releasing the target specific antisense conjugated compound trapping $Gd3^{+}$ transporter. The specification is silent about the generation of other diagnostic conjugates for tumor imaging using a genus of "cell penetrating transport

peptides which penetrate the plasma membrane". In addition there are enabling issues as each of the cell-penetrating peptides transport specific molecules, for example, Tat fragments internalize proteins such as RNase A, penetratin and transportan trasnport PNA suh as galanin receptor antisense (21-mer), signal-sequence based peptides internalize peptides such as SCH Tyr 317 region (12 residues) and others (see Lindgren et al, Exhibit A, page 100 Tabel 1). Hence it would require undue experimentation to one of skill in the art to make and use any of the claimed "cell-penetrating transport peptides" in transporting a PNA with the intended use of diagnosing a tumor.

At page 15 of Remarks, Applicants argue that "Applicants have amended claims 1 and 20 to limit the terms "address module" and "signaling module" in the claims to the subject matter that the examiner considers sufficiently supported and enabled by the specification. The applicants respectfully request that the rejection be withdrawn since the enablement requirement for the terms "address module" and "signaling module" is fully satisfied. Additionally, with regard to the "signaling module," the applicants note that the structure and synthesis of suitable Gd- complexes or Gd-conjugates are set out and readily obtainable from Caravan et al. without undue burden at the time the present application was filed'.

The Examiner refers Applicants to the reasons of record, as disclosed in the previous office action, and the reasons discussed in the paragraph above. In addition, it would require undue experimentation for the skilled artisan to make and use any of the broadly claimed compounds trapping Gd in the conjugate in order to minimize undesired interactions between the compounds trapping Gd and the rest of the conjugate or to specifically penetrate the plasma membrane in a target cell because the hydrophobicity of Gadolinium chelates conjugates and the

variations in hydrophobicity of the different Gd chelates (p. 2295, col. 2, paragraph 1; p. 2344, col. 2).

Claim Rejections - 35 USC § 103

Claims 1 and 20, as written, broadly encompass any address module, which is a cell-penetrating transport peptide able to penetrate the membrane. Similarly claim 30 broadly embraces any human cell-penetrating transport peptide able to penetrate the membrane.

Claim 1-3 and 15 remain rejected and claims 20, 30 and 31 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Braun et al., (US patent No. 6,821,948), in view Cavaran et al.,. Bioconjug Chem. 1999 :361-70).

Response to Applicants' arguments as they relate to rejection of claims 1-3, 15, 20, 30, and 31 under 35 USC § 103.

At page 17 of Remarks, Applicants argue that "Braun in view of Caravan does not teach each and every limitation that is recited in the claims of the present application. Braun teaches a conjugate for the transport of an active substance into a cell. In example 4, Braun teaches a peptide conjugate construct for the transport of a peptide nucleic acid (PNA) into the cell that is "anti-sense with respect to the rat's P2 promoter c-myc." (Braun, col. 8, ln. 18) As evidenced by the above citation, Braun teaches a peptide conjugate complex for transport into the cell that is antisense with respect to the P2 promoter c-myc DNA, because it hybridizes with the P2 promoter that is not transcribed into mRNA. As such, Braun discloses a PNA that is antisense to a DNA but not a PNA that is antisense to an mRNA. Therefore, Braun does not teach or suggest

an antisense PNA that hybridizes with an mRNA as is recited by the claims of the present application". Such is not persuasive.

Though the anti sense PNA with respect to rats P2 promoter c-myc taught by Braun et al. at col. 8, in Example 4, does not hybridize to a mRNA as the promoter sequence clearly signal the start for RNA synthesis, other disclosed embodiments of "**an active substance**" in the '948 patent include **antisense RNA, antisense oligonucleotides** and **PNA** (col. 4, line 16-19) which can be targeted to transcribed DNA sequences other than non-transcribed DNA sequences of promoter regions. Thus **the active substance** taught by Braun et al. is the same as **the address module** encompassed by claim 1 because both components of the conjugate are antisense PNA able to hybridize with the target mRNA. Thus it is unclear how Brown doe not teach or suggest an antisense PNA that that hybridizes with an mRNA as is recited by the claims of the present application.

At page 17 of Remarks, Applicants argue that "Braun teaches away from the use of the diagnostic agents used in the present application. Braun refers to a plethora of "diagnostic agents" but does not contain any reference to agents that are used for magnetic resonance imaging (MRI). (Braun, col. 4, 11. 5-22) In fact, though Braun states that "the active substance may optionally be labeled, e.g. radioactively, with a dye, with biotin, avidin etc.," none of the labels that are exemplified are related to the contrast agents that are used in MRI. (Braun, col. 4, 11. 10-11) Further, Braun does not teach or suggest making a PNA conjugate that is antisense to the mRNA of an oncogene "selected from group consisting of c-myc, c-ras, hern-, sstl or sst2" as is recited by the claims of the present application.

At the outset, the examiner notes that the instant claims are examined to the extent that read on the elected species, c-myc. As Applicants argue Braun does not recite the linking of a diagnostic conjugate to a compound trapping Gd. However, Gd is one of the contrasts agent used in radiological practice as disclosed by Cavaran. Braun discloses that an active substance in the conjugate such as oligonucleotides, mRNA, mTRNA, antisense RNA, antisense oligonucleotides can be optionally labeled with radioactive compounds for cell tracking to study gene expression in a living subject. Thus it would have been *prima facie* obvious for one of ordinary skill in the art to optionally label the conjugate of Braun to Gd chelates, including Gd- DTPA as disclosed by Caravan, to use into radiological practice as a contrast agent in MRI exams.

At page 18 of Remarks, Applicants argue that "Braun exemplifies peptides and nucleic acids as cargo molecules conjugated to a cell-penetrating transport peptide. Braun does not indicate that the use of metal chelates as suitable cargo molecules is possible. The lack of teaching in Braun in regard to metal chelates as cargo molecules conjugated to a cell-penetrating transport molecule is significant, since the chemical and physical properties of peptide or nucleic macromolecules conjugated to a cell penetrating peptide are very different from that of a metal chelate conjugated to a cell-penetrating peptide". Moreover, Applicants argue that "Braun does not teach or suggest a cell-penetrating transport peptide of human origin. All of the peptides disclosed by Braun are of synthetic construction". Such is not persuasive.

Applicants' position in regard to metal chelates as cargo molecules conferring unique chemical and physical properties to peptide or nucleic macromolecules conjugated to a cell penetrating peptide is not persuasive because Applicants' opinion is unsupported by any specific or real evidence, while the options of the skill in the art are given respectful consideration, in the

absence of any actual evidence of "unexpected results", the opinions of the inventor do not overcome a case of *prima facie* obviousness. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). See **MPEP § 716.01(c)** for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration. Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. MPEP 716.01(c). In relation to Applicants' argument that Braun does not teach or suggest a cell-penetrating transport peptide of human origin, the examiner notes that independent claims 1 and 20 do not recite the limitation. Hence the argument is not persuasive as they argue limitations that are not present in the claims.

At page 18 of Remarks, Applicants allege that "Caravan discloses that the "preparation of metal-chelate-dendrimer-antibody" constructs for use in imaging and radioimmunotherapy have been accomplished. (Caravan, pg. 2341, paragraph 2) Caravan also teaches that "[t]he challenge with regard to delivering sufficient quantities of paramagnetic label is substantial." (Caravan, pg. 2340, paragraph 3) The teaching of Caravan, however, is directed to the recognition of molecules on the surface of a cell. Caravan does not teach the cell- penetrating transport peptides according to the claimed subject matter of the present invention, which is a construct that is used to image the interior of the cell. The cell penetrating constructs of the present application do not recognize molecules on the surface of a cell, but directly interact: with the phospholipids of the membrane.

(See Derossi et al., Figure 2) Therefore, the antibody or tissue-specific molecular constructs taught by Caravan are functionally distinguished from the cell penetrating constructs of the present invention. Moreover, Caravan teaches away from the present invention by stating that a gadolinium chelate complex is unlikely to enter cells due to its non-hydrophobic character. (Caravan, pg 2295, 2nd col., 1st paragraph). [emphasis added]. Such is not persuasive.

Though Caravan at pg. 2295, 2nd col., 1st paragraph, indicates that because of the non hydrophobic nature of the Gd chelates, the conjugate may not enter the cell, the statement does not infer that the Gd chelate compounds cannot enter the cell. Indeed, the author present several examples wherein the various presence of hydrophobic groups on the metal chelates allows the uptake of the conjugates by the cell and thus penetration of the plasma membrane as claimed. For example, at page 2346, paragraphs 4-6, Caravan discloses how gadolinium-based agents can be up taken by the liver and transported from the hepatocyte into the bile. Thus in contrast to Applicants' assertion, gadolinium-based agents are not necessary deterred from penetrating into the cell. In addition to hydrophobic groups in the metal, the specific cargo such as an Ab or PNA will condition whether the gadolinium-based agent remains preferentially at the surface of the target cell or penetrates s the cell membrane.

Conclusion

Claims 1-3, 8, 10-15, 19, 20 and 22-35 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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